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Original Article

Prognostic factors and survival in patients with squamous cell carcinoma lymph nodes metastases from an unknown primary to the head and neck

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Abstract: Purpose: To analyze the clinicopathological characteristics, treatment modalities, and potential prognostic factors of cancer of unknown primary tumor (CUP) in a consecutivegroup cases. Methods: This retrospective study enrolled consecutive patients who were admitted to the Sun Yat-senUniversity Cancer Center between 1980 and 2011. Results: The key prognostic factors influencing the survival were the lymph nodes extracapsular extension (ECE), N classification, recurrence, emergence of primary tumor and treatment modalities. Multivariate analysis revealed that N classification and recurrence were independent risk factor for patient survival. Conclusions: N classification and recurrence were independent prognostic factor that influenced the treatment outcome. Our data indicate that combined surgery and postoperative radiotherapy for CUP offers the best chance for long-term survival.

Keywords: Cervical lymph node metastases, unknown primary tumor, squamous cell carcinoma, radiotherapy, surgery

Introduction

Cancer of unknown primary tumor (CUP) represents a heterogenous group of malignancies presenting with distant metastases without an identified primary tumor at diagnosis [1]. As a clinical entity defined by the exclusion of the presence of a primary tumor, the standardised work-up including meticulous medical history and clinical examination using modern diagnostic tools. Its estimated incidence ranges from 3% to 9% of all head and neck cancers, with squamous cell carcinoma (SCC) histology accounts for 53% to 77% of cases [2-4]. The three main aspects of this clinical entity are still a matter of controversy: the biology of the unknown primary tumor, theoptimal diagnostic algorithm, and the best treatment.Because of the rarity of CUP, few studies have addressed thetherapeutic management and outcome of this disease. The treatment of patients with cervical lymph nodemetastases from CUP is still controversially, the lack of randomized clinical trials comparingtreatment options is another importantpoint.

In this article, we report on the analyses of the clinicopathological characteristics, treatment outcomes, and potential prognostic factors in patients with cervical lymph node metastases from unknown primary tumor of SCC.

Patients and methods

Eligibility

In this retrospective investigation, the clinical records were included of all patients treated for CUP at the Department of Head and Neck Surgery, Sun Yat-sen University Cancer Center, Cervical lymph node metastases from CUP non-squamouscell carcinoma were excluded from this study.

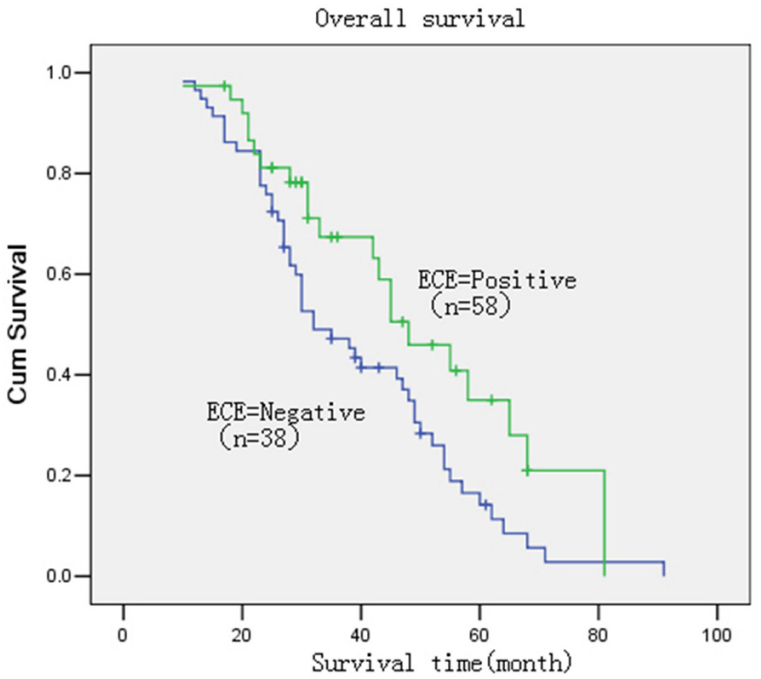

Figure 1. Kaplan-Meier curve with univariate analysis (log-rank) for patients with extracapsular extension positive versus negative for overall survival.

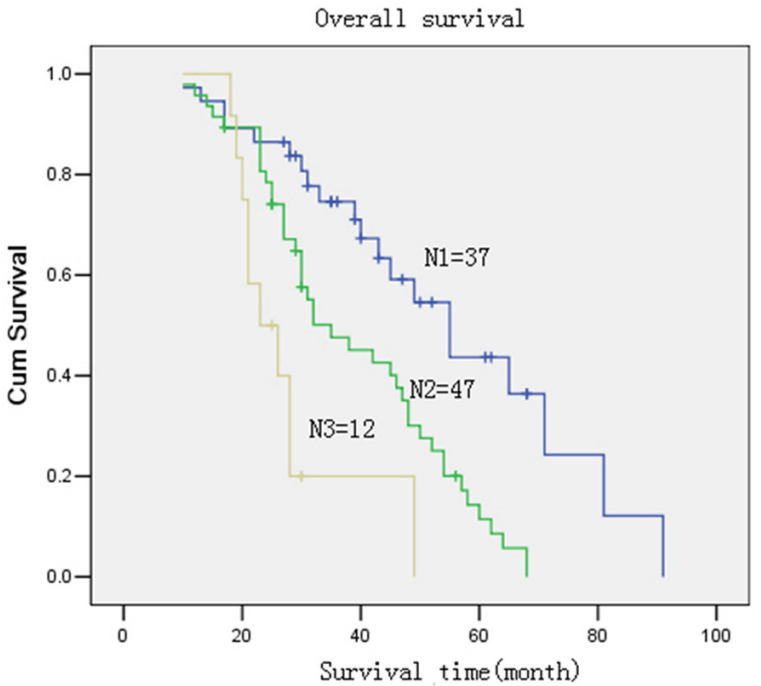

Figure 2. Kaplan-Meier curve with univariate analysis (log-rank) for patients compare among N stage for overall survival.

Informed consent was obtained from the patients, while ethics approval was obtained from the Institutional Research Ethics Committee of the Sun Yat-sen University Cancer Center.

The inclusion criteria for CUP were All patients under went otolaryngological examination exclude primary tumors and: (1) cervical squamous cell carcinoma metastasis verified by fine-needle aspiration cytology and/or by open biopsy, (2) no primary site detected by clinical, instrumental and surgical investigation, and (3) curative treatment intent.

The following data were registered for every patient: age at diagnosis, gender, nodal category, nodal region, histological findings, results of clinical, radiological and surgical investigations, treatment, recurrences, emergence of the occult primary or second primary tumor during the follow-up.

The routine diagnostic work-up comprised clinical examination and endoscopy of the aerodigestive tract, chest X-ray and standard haematological and biochemical tests; neck and abdominal ultrasonography were performed routinely. Further investigations (fiberbronchoscopy, gastroscopy, computed tomography, etc.) were done selectively in accordance with clinical indications. In few cases, under went 18F-fluorodeoxyglucose positronemission tomography.

Finally, after completion of the diagnostic work-up, between the years January 1980 and December 2011, the diagnosis of 'real' CUP was confirmed in 96 patients constituting 2.6% of all head and neck

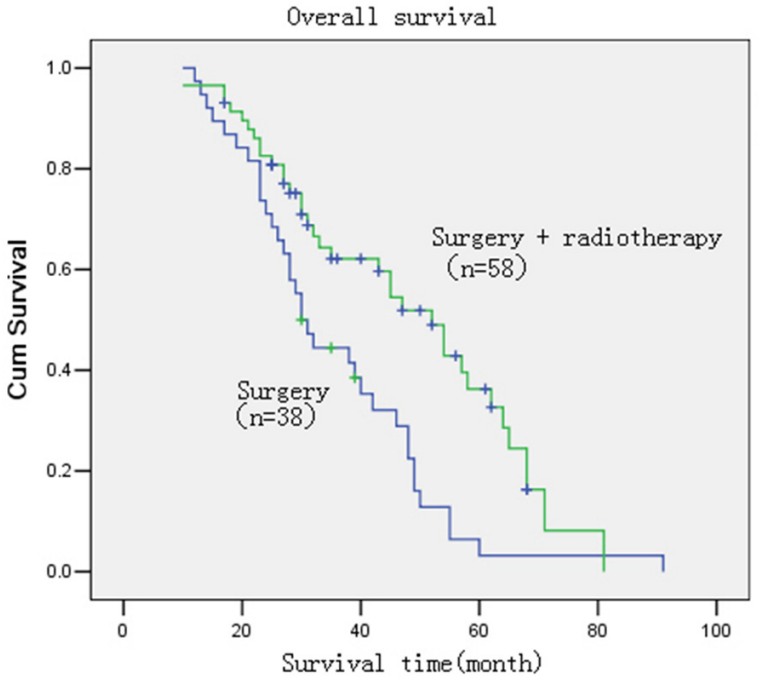

Figure 3. Kaplan-Meier curve with univariate analysis (log-rank) for patients treated with surgery versus surgery and radiotherapy for overall survival.

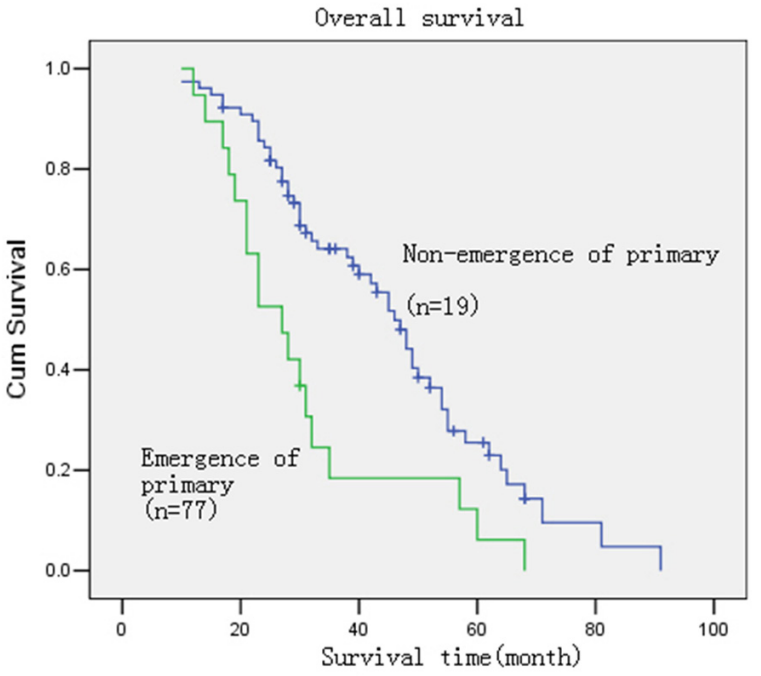

Figure 4. Kaplan-Meier curve with univariate analysis (log-rank) for patients-non-emergence of primary versus emergence of primary for overall survival.

SCC treated in our department in the same period. The main characteristics of the patients at diagnosis of CUP Median age were 54.7 years (range, 37-68 years), and the male to female ratio was 3:1. Patients treated were restaged according to the 2002 American Joint Committee on Cancer (AJCC) staging system.

Statistical analysis

The cutoff date of the last follow-up was November 30, 2012 for the censored data analysis. Survival was calculated from the date of diagnosis of CUP to the last date of contact and was analyzed using the standard Kaplan-Meier method. Tests of significance were based on log-rank statistics. Kaplan-Meier method was used for analysis of survival and the log-rank test was used to examine the difference between groups; Cox regression model was used for multivariate analysis. The statistical analysis was performed using SPSS 13.0 software (SPSS Inc., Chicago, IL). *P* value of < 0.05 was considered to indicate a statistically significant difference.

Follow-up data were collected from the out patient service and complementary data were obtained by telephone inquiry and follow-up letters. The routine follow-up program consisted of locoregional examination at 2-month intervals during the first year, 3-month intervals in the second year, 4-month intervals between the third and fifth years and every 6 months thereafter. All patients underwent annual chest radiography. The median follow-up period was 37.5 months (range, 10-91 months).

Treatment

Thirty-eight patients were treated with surgery for N1 without extracapsular spread patients (radical neck dissection, modified radical neck dissection and selective neck dissec-

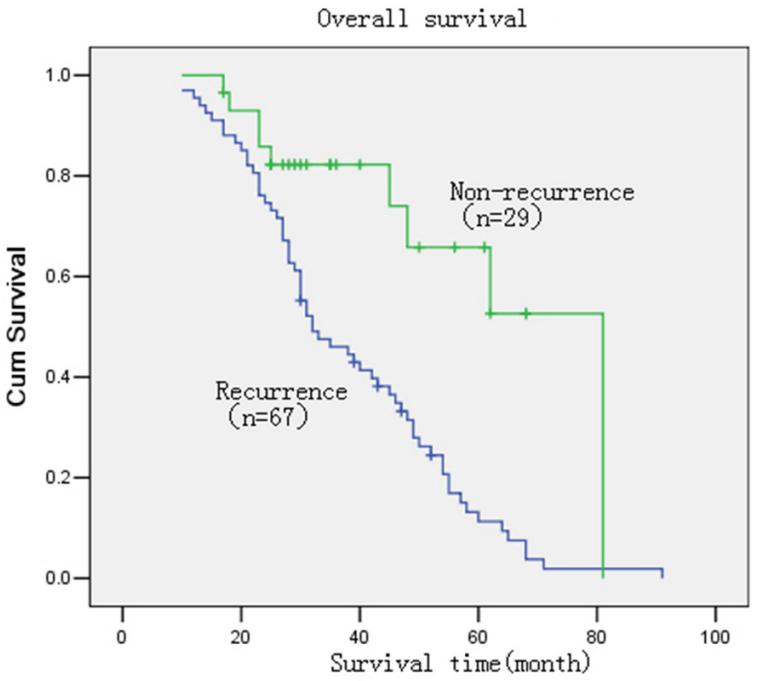

Figure 5. Kaplan-Meier curve with univariate analysis (log-rank) for patients with recurrence versus non-recurrence for overall survival.

tion), and the other fifty-eight patients underwent surgery and radiotherapy for N2, N3 without etracapsular spread cases, among the ninety-six patients, fifteen were given induction chemotherapy prior or after to surgery for extracapsular spread. Radiotherapy region dose: gross region dose 66-74 Gy (2.0 Gy/fraction, daily Monday-Friday) in 7 weeks. Mocosal dose 50-66 Gy to putative sites, consider higher dose to 60-66 Gy to particularly suspicious areas. Neck uninvolved nodal stations 44-64 Gy.

Results

Of theninety-sixpatients, nineteen patients emergence primary tumor in subsequent follow up, 71 patients died. The overall 3-year and 5-year survival rates of all patients were 54.9% and 21.2%, respectively. Univariate analysis revealed that the key prognostic factors influencing the survival of these patients were the lymph nodes extracapsular extension (ECE), N classification, recurrence, emergence of primary tumor and treatment modalities (**Figures 1**-**5**). There was no significant correlation with gender, the age when CUP was diagnosed (**Table 1**). In the Cox proportional-hazard regression model, N classification and recurrence were the independent risk factor; patients who were non-recurrence and lower N stage had a better prognosis than those recurrences after treatment and higher N stage at diagnosis CUP (**Table 2**). Other factors, includingage when CUP was diagnosed, lymph nodes extracapsular extension, emergence of primary tumorand treatment modalities had no influence on the survival of CUP.

Discussion

Patients with cancer of unknown primary presentwith metastatic disease and no identifiable site oforigin at presentation, Generally, the overall prognosis is poor. Despite thelong time periods they usually cover, the published seriesare generally small and hardly comparable due to theirheterogeneity arising from patient and tumor characteristics, treatment intent and the modalities used. Consequently, data addressing the optimal treatment approachdo not allow definitive conclusions, although the resultsof combined surgery and radiotherapy seem to be mostadvantageous [2].

The treatment policy in our departments gives preference to surgery and postoperative radiotherapy whenever feasible. Theadvantages of combined therapy are an improvedcontrol of neck disease, the possibility of reducing thetotal irradiation dose to obtain more tolerable treatment-related morbidity. Besides, ahistopathological examination of a resected specimen providesadditional information about the extent and aggressivenessof disease (pN stage, histopathological grade, extracapsularspread, and neoplastic emboli in lymphatic vessels). Thus, the radiation oncologistcan objectively consider assessed prognostic factors, so that under- or overtreatment is less likely. A review of the literature suggests the most promising results with this approach [5, 6]. Another advantage of combined therapy is

Table 1. Influence of clinicopathologic characteristics on the survival of 96 patients of squamous cell carcinoma lymph nodes metastases from an unknown primary to the head and neck

Variable	Cases (n = 96)	3-y survival	5-y survival	Chi-square value	*P* value
Gender				1.966	0.161
Male	73	0.513	0.194		
Female	23	0.664	0.266		
Age (years)				0.718	0.397
≥ 55	51	0.478	0.239		
< 55	45	0.626	0.204		
N stage				18.476	0.000
N1	37	0.746	0.437		
N2	47	0.476	0.115		
N3	12	0.20	0.000		
Extracapsular extension				4.586	0.032
Positive	58	0.472	0.142		
Negative	38	0.674	0.350		
Recurrence				10.545	0.001
Yes	67	0.460	0.113		
No	29	0.822	0.658		
Treatment				8.566	0.003
Surgery	38	0.444	0.032		
Surgery+radiotherapy	*58*	*0.621*	*0.363*		
Primary tumor				11.202	0.001
Emergence	19	0.186	0.061		
Non-emergence	77	0.641	0.255		

improved control of neck disease. This is clearly evident from the report of Davidson et al. [7].

The other proposed treatment options for neck metastases include neck dissection alone, radiotherapy alone, or neck dissection with postoperative radiotherapy. Some authors advocate single-modalitytherapy for patients with N1 and N2 a disease without lymph nodes extracapsular extension [9]. Although a selection bias cannot be excluded, neck dissection performed after radiotherapy showed evidence of nodal disease in up to 44 % ofpatients [8, 9-11]. In this study, 58 patients enroll in the proposed treatment principle, 3 year survival was 54.9% similar resultsas documentreports.

In this series, overall survival was strongly associated with the presence of ECE. This correlation is consistent with other reports [2, 12, 13]. A recent review showed that the prognosis in individuals with ECE of the CUP incervical lymph nodes is quite poor; moreover, ECE seems to be the most important prognostic fact or inpatients with cervical metastasis, in relation to bothlocal recurrence and distant metastasis [14]. According to other authors, an involvement of levels IV and V was associated with aworse prognosis in multivariate analysis. This may bedue to a higher rate of distant metastases observed inthese patients [4, 15, 16]. We have no proper explanationfor this, norfor the high rate of bilateral metastases.

The predominant pattern of treatment failure in ourstudy cohort was regional recurrence within the dissected neck or contralateral metastases to the undissected neck, which occurred in 67 patientsand accounted for 69% of all treatment failures. All patients had adverse pathological prognostic factors, namely ECS and/or advanced nodal disease, in this study, ECS positive occurred in 58 patients which may be a reason for local recurrence. Outcomes were particularly poor in patients with macroscopic ECS and pN2 or pN3 disease, with treatment failing in the neck in 69% of these patients. These selected patients may benefit frommore aggressive treatment, in particular postoperative radiation. This is particularly important given the highrate of successful salvage experienced in patients with recurrent disease in our series.

The emergence of a subsequent primary tumor is amain topic in neck metastases from an unknownprimary tumor. Several studies showed that the subsequent detection of a primary tumor is associated with a poorer prognosis [17-19]. Prophylactic mucosalirradiation is performed to treat the putative site of the primary tumor. In our series, the actuarial rate of developing head and neck primary tumors at 5 years was 19%. This rate is comparable to those recorded in other series in which comprehensive irradiation was performed [5]. Con-

Table 2. Results of Cox proportional hazards regression model for 96 patients with squamous cell carcinoma lymph nodes metastases from an unknown primary to the head and neck

Factors	Neck dissection group (n = 136)		
	Positive	Negative	*P*
T classification			0.276
T1	10	57	
T2	14	55	
Pathologic grade			0.142
Well	18	67	
Moderately	3	37	
Poorly	3	8	
Thickness			0.045
< 4 mm	1	26	
> 4 mm	23	86	
Vascular invision			0.002
No	13	95	
Yes	11	18	

versely, this strategy is associated with side effects due to the increased irradiated volume [19]. For that reason, other authors suggest a limited-field radiotherapy treating the ipsilateralneck only. Some authors reported that ipsilateral radiotherapy considerably reduced the risk of having an emerging mucosal primary tumor when compared with patients treated with surgery alone [15].

Conclusion

In conclusion, patients presenting with cervical metastasis froman unknown primary tumor remains a therapeutic challenge. The survival results favourably comparable to those reported else where and obtained by asingle modality approach, as observed in our study, strongly support the use of combined therapy. However, more aggressive therapy should be offered to selected patients, namely, those with bulky neck disease (pN2 and pN3) and, inparticular, patients with macroscopic ECS. In the absence of randomized trials, prospective trials analyzing the therapeutic ratio are urgently needed.

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Disclosure of conflict of interest

None.

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